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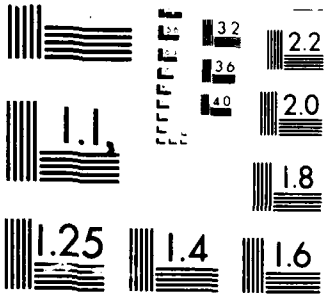

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IMPERMEANT SOLUTES AND CELLULAR CALCIUM METABOLISM IN PATHOGENESIS OF ACUTE RENAL FAILURE

Annual Report

Robert W. Schrier, M.D.

April 1984

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3146

University of Colorado School of Medicine
Denver, Colorado 80262

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) IMPERMEANT SOLUTES AND CELLULAR CALCIUM METABOLISM IN PATHOGENESIS OF ACUTE RENAL FAILURE		5. TYPE OF REPORT & PERIOD COVERED Annual Report 05/01/83-04/30/84 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Robert W. Schrier, M.D.		8. CONTRACT OR GRANT NUMBER(s) DAMD17-83-C-3146
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Medicine, C281, School of Medicine University of Colorado Hlth. Sci. Ctr. 4200 E. 9th Ave., Denver, CO 80262		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102A.3M161102BS10.BA.275
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND Fort Detrick, Frederick, MD 21701-5012		12. REPORT DATE April 1984 13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Acute renal failure, dogs/rats, ~~ischemia~~, norepinephrine, calcium, verapamil, nifedipine, mannitol

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Verapamil infused into the renal artery at low doses that do not influence contralateral renal function nor systemic hemodynamics prevents or attenuates markedly the severity of ischemic (norepineprine-induced) acute renal failure in ghe dog. When given before norepinephrine, glomerular filtration rate returns to normal at 24 hours and cellular morphology is nearly normal. When given for 2 hours after norepinephrine, glomerular filtration rate returns to 50% of normal at 24 hours. Mannitol given intravenously for 30 minutes prior to norepinephrine prevents mitochondrial respiratory depressin and improves glomerular filtration

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SUMMARY

During the first year of this contract (05/01/83-04/30/84), the effects of verapamil administered intrarenally in the dog before or after an intrarenal norepinephrine infusion was completed and a second dissimilar calcium channel blocker, nifedipine, was administered after norepinephrine. Norepinephrine alone, in this study, caused acute renal failure but this was prevented by verapamil given before norepinephrine and markedly attenuated by verapamil or nifedipine administered after norepinephrine. This work was submitted for publication on August 12, 1983. Moreover, we also investigated the protective effect of mannitol on mitochondrial calcium handling in the dog model of norepinephrine-induced acute renal failure. That study demonstrated that mannitol, besides acting as a vasodilator in this model and an osmotic diuretic which flushed debris from the nephron - effects we had previously reported, also prevented mitochondrial and tissue calcium overload during reperfusion after ischemia. We also began exploratory studies into the mechanism of gentamicin-induced acute renal failure and found initially that like ischemia calcium overload was associated with progressive renal failure. Finally, we performed some initial experiments investigating allopurinol and mannitol as agents whose cellular protection might be related to free radical scavaging effects (mannitol) or to preventing free radical formation (allopurinol).

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BODY OF REPORT

Acute renal failure continues to be a medical problem often occurring after severe trauma and hemorrhage or shock. In addition, antibiotics, often given to patients injured by trauma or following surgery, can compound renal dysfunction arising from the above causes. Mannitol and other diuretics which increase renal blood flow and cause a solute diuresis are more effective than those which simply cause diuresis (1). The present study investigated, therefore, the protective effects of mannitol on acute renal failure. Attention was directed at its role in preventing cellular calcium overload since calcium and cellular injury have been correlated in many forms of ischemic and toxic injury to other organs. Little attention had been directed at this relationship in the kidney, however. Furthermore, we examined the protective effects of the calcium channel blocker, verapamil, as a protective agent in preventing ischemic acute renal failure. These two major projects were essentially completed by the end of the first year of the contract and preliminary studies into the mechanism of the nephrotoxic effect of gentamicin were initiated. A summary of the major results will be reported here; the gentamicin studies are planned to be reported on in the second annual report.

Verapamil administered intrarenally before (30 minutes) norepinephrine or for 2 hours after norepinephrine prevented the low glomerular filtration rate that is usually seen at 1, 3 and 24 hours post-ischemia. Verapamil was administered at 5 μg/kg/min in these studies and with pretreatment, glomerular filtration rate was normal at 24 hours. Renal morphology was well preserved and sodium reabsorption and urinary concentrating ability was improved, the latter being functional signs of less injured tubules. We have been requested to perform confirmatory studies with another calcium channel blocker; these are underway using nifedipine. We noted in these studies that renal blood flow improved more quickly and remained elevated longer in dogs given verapamil after compared to before norepinephrine. The glomerular filtration rate, however, was improved more so with verapamil pretreatment. Therefore, simply improving renal blood flow is not the sole determinant in preventing cellular injury. Verapamil also reduced cellular calcium overload, prevented mitochondrial calcium accumulation, and prevented depressed mitochondrial respiration. Verapamil treated kidneys had normal mitochondria viewed with electron microscopy and intact brush borders. There was no evidence of the swelling or necrosis which normally attended ischemia, lending credence to the suggestion that calcium does play a role in cell injury in the kidney like that seen in other organs after ischemia (2).

The mannitol infusion studies were used to address the question of whether, by reducing cell swelling and membrane leakiness, mannitol might also reduce cellular calcium overload. In these experiments mannitol was infused for 30 minutes prior to norepinephrine. It was found that mannitol treated dogs had better mitochondrial respiration and less calcium overload during reflow compared to untreated dogs. These results and our previous data suggested that mannitol exerts a protective effect against renal ischemia functional injury in multiple ways. First by improving renal hemodynamics, second by preventing tubular obstruction due to its osmotic diuretic effect and third by decreasing the calcium influx which would generally overload swollen and ischemic cells. These results have been submitted for publication (3).

The early pilot studies on gentamicin nephrotoxicity are too preliminary to report upon.

Conclusion and Recommendations

We conclude that calcium overload induces cellular injury in ischemic acute renal failure and that this can be prevented by mannitol given before ischemia or by verapamil given before or after ischemia. It is recommended that these agents should be investigated to determine if they can be used as efficaciously after hypotensive shock or trauma especially since verapamil might cause a decrease in either systemic vascular resistance, if given intravenously, or cardiac output. Low doses of verapamil could, even if cardiac output or systemic vascular resistance is reduced modestly, reduce renal blood flow modestly leading to less calcium delivery to injured tissue. Thus, the advantages of giving such small doses of verapamil need to be vigorously explored.

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3. Schrier RW, Arnold P, Gordon J, Burke TJ: Protection of mitochondrial function by mannitol in ischemic acute renal failure. Am J Physiol, submitted.

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